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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,254	04/12/2004	Peter A. Kiener	10271-060-999	5469

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	
MAIL DATE	**DELIVERY MODE**
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,254	KIENER ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,9-14,16,17,27,28 and 33-42* is/are pending in the application.

4a) Of the above claim(s) *33-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,9-14,16,17,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 7, 9-14, 16, 17, 27, 28 and 33-42 are pending.

Claims 33-42 have been withdrawn as being drawn to a nonelected invention. The elected claims were drawn to a method of treating a non-neoplastic hyperproliferative cell or excessive cell accumulation disorder in a patient which is an *in vivo* method of treatments. Claims 33-42 read on in vitro methods and thus are outside the scope of the elected invention.

Claims 1-3, 7, 9-14, 16, 17, 27 and 28 are currently under examination.

Objections to Specification withdrawn

The objections to the specification are withdrawn in view of Applicant's amendments to the specification and the submission of the replacement Abstract.

35 USC § 112 1st paragraph rejection maintained

The rejection of claims 1-3, 7, 9-14, 16, 17, 27 and 28 for failing to comply with the enablement requirement is maintained.

Applicants argue that the specification and state of the art at the time of filing demonstrate:

I. An art accepted model of fibrosis, the bleomycin-induced fibrosis model, existed;
II. EphA2 is associated with fibrosis;
III. Agonizing EphA2 is a treatment for fibrosis.

Applicants argue that Chua teaches the acceptance and the importance of the bleomycin induced fibrosis model in the understanding of the pathology of lung

fibrosis. Applicants argue that correlate EphA2 upregulation with the onset of lung fibrosis in Example 6.8 of the instant specification using the *art* accepted bleomycin-induced fibrosis lung epithelial model. Applicants also argue that the specification of the present application presents working examples demonstrating the association of EphA2 expression with fibrosis, the correlation of EphA2 activity with the progression of fibrosis and the reduction of fibrosis with agents that agonize EphA2 activity in vitro.

Applicants arguments have been fully considered but are not persuasive.

The claims are drawn to a method of treating fibrosis in a patient comprising administering a therapeutically effective amount of an EphA2 agonistic agent, wherein said EphA2 agonistic agent binds EphA2. The specification discloses an in vitro model of fibrosis in which transformed bronchial epithelium cell were treated with bleomycin. (page 89 lines 12-17). The specification also discloses that EphA2 protein expression was upregulated in the transformed cells 24 hours after treatment with bleomycin. (page 92, lines 15-27). The specification also discloses that EphA2 is expressed in lung epithelium in vivo. (Figure 2).

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. In re Wands, 8 USPQ2d 1400 (CA FC 1988). Whether under due experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. (Id.).

The amount of knowledge in the art concerning the successful treatment of fibrotic lung disease is low especially the treatment of fibrotic disease *in vivo* with antibodies. Chua et al alluded to the lack of any adequate treatment for pulmonary fibrosis. (page 12 2nd column 4th paragraph). Wang et al (Biochemical Pharmacology, 200, 60:1949-1958) states that induced pulmonary fibrosis is a crippling disease and responds poorly to current therapy.

Applicants have not demonstrated the involvement of EphA2 in fibrosis *in vivo*. As mentioned previously, those of skill in the art recognize that in vitro assays and or

cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. The specification discloses that EphA2 is expressed in lung epithelium in vivo but did not demonstrate any change in expression or activity of EphA2 in fibrosis or that any antagonist of EphA2 reduces fibrosis in a patient.

Applicants have not demonstrated the use of an art accepted in vivo model of fibrosis. The bleomycin model of fibrosis of Chua et al, referred to by Applicants, is an in vivo model of fibrosis which is distinct from the in vitro model of fibrosis used in the present application. Chua et al when discussing in vivo models for pulmonary fibrosis stated that "in vitro systems are limited to probing particular cellular or molecular responses that in isolation are too remote from actual lung pathophysiology." (page 10, 2nd column, 2nd paragraph).

Applicants also argue that it was well known as of the filing date that a large number of antibody therapeutics were already in preclinical trials and in clinical use as evidenced by Reichert et al. However, this not address the issue that the treatment of disease with antibodies in vivo is generally unpredictable. More antibodies are being used in clinical studies but the development of antibodies for treatment in vivo is still considered to be unpredictable as indicated by White et al. Furthermore, Applicants arguments are not commensurate in scope with the claims which recite a method of reducing fibrosis in a patient comprising administering an effective amount of an EphA2 agonistic agent.

Applicants also refer to Board of Patent Appeals and Interferences (BPAI) decisions of Ex Parte Boutin and Ex parte Forstova to support there claim that in vivo data is not required for enablement of their claims. The claims in the two Board decision relate to a methods of delivering a nucleic acid composition to a cell. The

present claims are drawn to a methods of reducing fibrosis in a patient which are clearly distinct form the claims under review in the Board decisions.

Applicants also refer to U.S. Patent No: 7,175,844, U.S. Patent No:7,172,757 and U.S. Patent No:6,652,856 '757 patent for the proposition that an *in vivo* working model is not a requirement for enablement form claims drawn to a method of treating fibrosis in a patient with an antibody. As mentioned above whether under due experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.

Given the disclosure of the specification and the teaching in the art that indicates the unpredictability of treating fibrosis in a patient, the lack of data concerning the involvement of EphA2 in fibrosis *in vivo* and the lack of in vivo working examples of reducing fibrosis in vivo with an EphA2 agonistic agent, one skilled in the art could not predictably reduce fibrosis in a patient with an EphA2 agonistic agent.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

The rejection of claims 11 and 13 for failing to comply with the enablement requirement is maintained.

The specification and Applicants Affidavit fails to provide sufficient enablement for the claimed methods drawn to methods of using specific antibodies, Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233. It is not clear from the disclosure that the deposits of Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233 meet all the criteria set forth in MPEP 2410.02 items 1-3. Specifically,0095 on pages 25-26 of the specification and Applicants Affidavit fails to indicate that all restrictions on the availability to the public of the deposited antibodies will be irrevocably removed upon the granting of a patent. Assurance of compliance may be in the form of a declaration or averment under oath.

A statement from Applicants or Applicants attorney indicating that "all restrictions on the availability to the public of the deposited antibodies will be irrevocably removed upon the granting of a patent" would obviate this rejection.

Summary

Claims 1-3, 7, 9-14, 16, 17, 27 and 28 stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
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/Misook Yu/
Primary Examiner, 1642